UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 6 Cases*	

EXPERT REPORT OF TERENCE J. COLGAN, M.D.

This document relates to: Wave 5 Cases

In Re: Ethicon, Inc.
Pelvic Repair System
Products Liability Litigation

Expert Report of Terence J. Colgan, MD.

Qualifications –

I am a duly qualified medical doctor, licensed to practice in the Province of Ontario, Canada. I obtained my medical degree from the University of Toronto in 1977. After a year's internship I embarked upon a residency in Anatomical Pathology at the University of Toronto which successfully led to specialty certificates in Anatomical Pathology from both the Royal College of Physicians and Surgeons of Canada and the American Board of Pathology. In addition to the above qualifications I have undertaken additional fellowship training in gynecologic and breast pathology at the Armed Forces Institute of Pathology in Washington, D.C. and in electron microscopy at McMaster University in Hamilton, Ontario. I am a member of a number of medical societies including the United States and Canadian Academy of Pathology and the International Society of Gynecological Pathologists. For over 20 years I have been active in the Committees and work of the College of American Pathologists (CAP) which is devoted to improving quality in pathology practice and laboratory medicine and am the recipient of the 2017 CAP Educational Award.

Since 1983 my pathology practice has been focused on the pathologic assessment of specimens from the female genital tract, which is known as gynecological pathology, and of cytopathology specimens. From 1997 to 2000 I was Head of Surgical Pathology at the University

Health Network in Toronto Canada. Currently I am Head of the Sections of Gynecological and Cyto-pathology at the Sinai Health System in Toronto. The Sinai Health System is recognized as a center of excellence in women's health care and research. In addition, I am a consultant in gynecologic pathology at LifeLabs, a diagnostic laboratory company. I see over 5000 cases per annum, including resected mesh specimens, and provide these consultations to surgeons in the Sinai Health System and Ontario community. In addition, I provide an expert consultative service regarding gynecologic pathology issues for pathologists throughout the province of Ontario and Canada. In addition to these clinical responsibilities I undertake both independent and collaborative research and have contributed over 150 articles to the peer-reviewed research literature. Two of these papers examined the inflammatory and healing reactions in the gynecologic tract following embolic therapy and hysteroscopic surgery.[1, 2] From 2009 to 2016 I served as an Associate Editor of the American Cancer Society's *Cancer (Cytopathology)*. In this capacity I was responsible for selecting scientific reviewers of submitted scientific papers and ultimately for assessing adherence to the scientific method and the veracity and importance of claims and conclusion. Recommendation for acceptance or rejection of submitted manuscripts was based upon these assessments. I also serve on the Editorial Board of the International Journal of Gynecological Pathology and Archives of Pathology and Laboratory Medicine. I teach both in the University of Toronto residency and fellowship training programs and in national and international venues. A complete *Curriculum Vitae* is attached in Exhibit A.

I have been retained on prior occasions to advise and provide opinions concerning claims for medical malpractice. These retainers as an expert witness have been at the request of both defense and plaintiff attorneys, and have occurred both in Ontario and occasionally in the United States.

I have been asked to review medical literature, Dr. Iakovlev's research, and his written report in the matter of allegations regarding possible effects of the placement of mid-urethral mesh slings in the treatment of urinary stress incontinence. These materials are attached in Exhibit B. I hold the opinions that follow to a reasonable degree of medical and scientific certainty and/or probability.

The practice of surgical pathology – technical aspects

The practice of surgical pathology has evolved since the late 19th century. Standardized methodologies have been developed and widely implemented. An understanding of these methodologies is important to assess the merits of claims and conclusions from surgical pathology studies.

Resected human tissues may show some retraction following resection. Following resection human tissues commence decomposing within minutes and hours of removal due to degradation by endogenous enzymes. Decomposition results in a loss of microscopic structure which is required for microscopic examination. Solutions known as "fixatives" halt this decomposition process. Although a variety of tissue fixatives are available resected tissue specimens are usually placed into a watery solution, formalin. Formalin acts to "fix" the tissue and preserve morphologic features through the prevention of tissue breakdown.

Formalin is an aqueous solution, a 4% weight to volume of formaldehyde. Through reactions with both proteins and nucleic acids formaldehyde stabilizes tissues.[3] Formalin will not fix some types of molecules. Formalin has little effect on carbohydrates. Indeed, glycogen, a sugar, is soluble in the aqueous solution. Lipids (fats) are preserved only if the formalin solution contains calcium. The formalin fixation that occurs in the short fixation times of modern

surgical pathology (hours to 2 days) is primarily due to the formation of hydroxymethyl groups with proteins.

Formalin fixation has a number of secondary effects which produce recognizable artifacts. Formalin induces swelling (rigidity) and hardness of tissues.[4, 5] For example, a segment of fresh, unfixed bowel is very pliable and soft. After formalin fixation a bowel segment assumes a more rigid, inflexible configuration, similar to a soft garden hose. Some shrinkage occurs with formalin fixation[5] and prolonged fixation is associated with additional shrinkage.[6] Fixed tissue will often not retain the shape and pattern that was actually present in vivo since the tissue will conform to the specimen container size and shape. For example, a uterus forced into a tight fitting container might appear to be severely bent or flexed, a condition which did not exist within the woman’s body. If large specimens are compressed into a tight-fitting container the fixed tissue the specimen may actually assume the shape of the container. A compressed length of bowel may assume the appearance of the bottom of a bucket.

The selection of tissue for microscopic examination is the next stage in surgical pathology processing. The gross (macroscopic) specimen is examined and described. This process is known as “grossing”. Small “bite”, needle or punch biopsies from the gastrointestinal and respiratory tracts and skin will be submitted in their entirety for microscopic examination. It is not practical to submit entire large specimens, such as bowel or gynecologic resection specimens, so only sampling can be undertaken. The goal is to select representative sections for microscopic analysis.

Formalin fixed tissue can only provide a suitable microscopic section with intact structure if all water is removed through successive alcohol baths, and replaced by liquid paraffin which is allowed to harden. The ensuing paraffin block retains tissue structure, and is capable of

providing multiple microscopic sections which are mounted on glass slides. This entire process is known as "histologic processing" and it has been designed for the analysis of tissue. Although essential to the modern surgical pathology laboratory, histologic processing also has secondary artefactual effects, as well. The dehydration, clearing and wax impregnation causes additional shrinkage of tissues.[4] In smaller biopsies this shrinkage may be imperceptible and inconsequential. Measurement of dimensions of sections of larger specimens, however, can be appreciably altered. In these cases it is generally accepted that formalin-fixed paraffin embedded tissue sections can produce a 10% shrinkage from the actual fresh tissue size. Paraffin embedded tissue which entails high temperatures and multiple solvents may adversely impact the integrity of proteins and other molecules of the specimen.[7]

A fixative may interact with all phases of processing and staining during subsequent histologic processing. Formalin alters the protein composition of tissues, so subsequent histochemical stains must be able to perform consistently with these fixed tissue proteins. In general, formalin fixation favors the staining of acidic structures, such as nuclei, with basic dyes, and diminishes the effect of acid dyes on basic structures, such as the cytoplasm.[4] For diagnostic pathology it is important that staining results are consistent so morphologic features can be assessed routinely.

Immunohistochemistry is a more technically demanding and advanced staining method which requires a specific reaction between an antibody and a desired target. Immunohistochemistry can be impaired by both fixation and histologic processing and additional procedures may be required to restore detectable protein, known as "antigen retrieval".[7] Prolonged periods of fixation may produce a special challenge in immunohistochemical staining since the target antigens may have undergone cross linking.[5] Even sophisticated methods of

antigen retrieval may not lead to successful immunohistochemistry of specimens subjected to prolonged emersion in formalin.

In summary, the essential pre-interpretive (pre-analytic) surgical pathology processes of formalin fixation, grossing, and histologic processing are accompanied by numerous artifacts. The subsequent paraffin block and slides are significantly transformed from the original submitted fresh tissue. Efforts are made to standardize all possible artifacts. Interpretations and conclusions in surgical pathology must be made bearing in mind these limitations and secondary effects.

The practice of surgical pathology – interpretation follows clinicopathologic studies

The clinical significance of a surgical pathologic finding is not evident on first viewing ("prima facie"). Before any surgical pathology finding can be used to predict or correlate with a clinical manifestation or outcome, supportive clinico-pathologic data must be available which clearly establish this relationship. Early in the development of the discipline of surgical pathology these data were often derived from autopsy studies. Subsequently, surgical pathology became valuable because its findings could definitively identify the cause of a clinical problem hitherto unexplained. For example, the cause of a mass presenting in patient with a history of cancer could have a number of origins. Pathologic examination of the resected mass was able to identify the mass to be an abscess, and not a recurrence of the cancer. In another example, modern day pathologic examination of a resected endometrial polyp may identify an unsuspected endometrial cancer.

In modern times clinico-pathologic studies have enhanced the contribution of surgical pathology to patient care in that clinical manifestations and likely outcomes of some diseases may be anticipated by surgical pathology findings. For example, the surgical pathology findings

in the resected uterus, ovaries, and fallopian tubes from women with endometrial cancer are used to predict likely outcomes and potential sites of recurrence. Appropriate post-surgical treatment can then be offered to the woman.

Clinico-pathologic studies often require painstaking study of large populations of patients with careful attention to exclude possible confounding factors. To continue with the endometrial cancer analogy, numerous clinic-pathologic studies of endometrial cancer resection specimens over decades have been performed, and there is a broad consensus among the profession about key morphologic findings that should always be assessed. The College of American Pathologists has developed Cancer Protocol Templates to assist in the reporting of these assessments.

In the absence of clinico-pathologic data such as that which would be found in peer reviewed studies, the clinical significance of a surgical pathology finding is uncertain. Surgical pathologists in general do not attempt correlations regarding pain, loss of function, or disability. In this situation the surgical pathology report should note the objective finding, but no reliable statement can be made regarding its clinical significance. For example, in gynecologic pathology it would be common to note that a "Fibrotic scar" was evident in a vaginal resection specimen, but no attempt would be made to infer the clinical manifestation of pain or other symptoms in the patient.

Surgical pathology findings and healing.

Surgical pathologists will frequently observe and report findings that are secondary to tissue damage and subsequent repair without any history of prior surgery. For example, gynecologic pathologists often note ulcers (or erosions) of the uterine cervix with associated acute inflammatory exudate in hysterectomy specimens which have been performed for uterine

prolapse. In this situation the cervix often may also show a protective response characterized by thickening of the covering epithelium and acquisition of a new surface layer (keratinization). Vaginal portions may also accompany the uterus, and these portions show varying degrees of both chronic and acute inflammation.

Surgical pathologists may also observe the healing reaction secondary to surgical procedures. At a surgical site blood clot will occur. In addition, tissue may be damaged during surgery and during the acute inflammatory process. Both the clot and damaged tissues need to be replaced and repaired by scar. Two types of cells are primarily responsible for this repair. New blood vessels are formed. These small vessels are accompanied by fibroblasts which are responsible for laying down extra-cellular fibrous tissue, and become active at the periphery of viable tissue, and move into the clot and damaged tissue. The numerous small in-growing capillaries (vessels) and fresh loose fibrous tissue with active fibroblasts which is developed over time are known as “granulation tissue”, a repair tissue. Adipose or fatty tissue is not considered to be a reparative tissue. Nerve in growth occurs. Contractile filaments develop within the fibroblasts, leading to a new cell type, the myofibroblast. Myofibroblastic contraction and maturation of the collagen leads to contraction of the wound. The new fibrous tissue continues to mature for weeks, months, and even longer. Vascularity and cellularity decrease. Collagen re-organization and substitution occurs to form a stable scar. Foreign bodies may be incorporated within the scar.

Although the above inflammatory and reparative processes are labeled as “pathologic” since they are a result of injury and a deviation from normal tissue physiology, these processes are essential to restore tissue integrity and function following major surgery with associated use of sutures and any residual foreign fibers. A number of factors may alter the quality or adequacy

of the reparative process including infection, nutrition, steroid therapy, local pressure or torsion, and poor blood perfusion.

Surgical pathology and foreign material in the human body.

Surgical and gynecologic pathologists routinely observe the body's reaction to foreign material from prior surgery or biopsy. Foreign bodies commonly seen in surgical pathology include suture material, residual surgical fibres, therapeutic embolic material, worn hip and knee prostheses, and surgical meshes. Dead (necrotic) native tissue may also elicit a similar response. Foreign material elicits both non-specific acute and foreign-body inflammatory responses that are well described in classic pathology texts.[8] The immediate reaction to a foreign-body is envelopment by proteins. Subsequently, inflammatory mediators prompt the migration of acute inflammatory cells from vessels into the surrounding connective tissue. Neutrophils, also known as polymorphonuclear cells, are the major cellular component of this acute reaction. Since surgical implants are rarely removed in the few days following surgery this initial acute inflammatory response is rarely observed by pathologists in the diagnostic laboratory.

Increasing numbers of macrophages or histiocytes, another type of white cell, accumulate within days of implantation in an attempt to ingest and destroy the foreign material. This destruction occurs through the secretion of a variety of substances by macrophages. Macrophages become the predominant cell population, and the number of neutrophils diminishes. Macrophages may transform into two additional cell types. If the macrophages develop abundant, pink cytoplasm then it is labelled as an "epithelioid" cell. Granulomas are groups or clusters of epithelioid cells. Lymphocytes and plasma cells, other types of white cells, may accompany granuloma formation. Secondly, macrophages may merge and form foreign multinucleated giant cells, also known as foreign-body giant cells. Both granulomas and foreign

body giant cells are found in long-term (chronic) inflammatory reactions to foreign material and may persist indefinitely.

In addition to the attempt to destroy foreign material the adult body seeks to re-establish tissue integrity. Although some tissues are capable of regeneration with complete restoration of form and function in many tissues repair can only be accomplished through the formation of a scar. A scar is formed through the laying down of new fibrous tissue, the major constituent of which is extra-cellular collagen.

Surgical pathology findings and explanted mesh specimens.

Studies have been undertaken to identify the body's reaction to implanted meshes and have confirmed a persistent foreign body reaction to mesh as described above.[9 - 14] Resected mesh specimens reveal chronic inflammatory cells around mesh filaments along with foreign body cells, granulomas and fibrosis. Fibrous tissue is laid down about, and within the mesh. One study identified that most levels of inflammatory response to abdominal wall mesh decrease over time suggesting a more favorable tissue response with increasing implantation interval.[9] Vaginal punch biopsies performed one year following polypropylene mesh insertion have also demonstrated a "mild but persistent foreign body reaction".[15] The most comprehensive histopathological study of explanted meshes from humans concluded that a foreign body reaction to vaginal mesh is apparent in about 90% of excised slings and may be ubiquitous.[10] The large majority of excised slings show mild to moderate fibrosis. In vivo studies of implanted meshes in animal models have shown a similar inflammatory and healing reaction.[16, 17] This is an expected reaction to a foreign body.

Explanted mesh specimens and clinic-pathologic correlations.

A recent study was undertaken to explore whether different histological changes were found in patients whose slings were removed for pain in comparison to patients whose slings were removed for other reasons. This clinico-pathologic study did not identify an association between pain and fibrosis in explanted mesh specimens. Fibrosis and foreign body reaction were similar in patients undergoing mesh excision for voiding dysfunction and pain and/or mesh exposure.[10] Levels of inflammation were higher in the voiding dysfunction alone group than in those with pain/mesh exposure with and without voiding dysfunction. Another clinic-pathologic study of explanted meshes from abdominal wall hernia repair found no significant differences in measures of inflammation between mesh removed for pain and mesh removed for hernia recurrence.[9] Similarly, a review article co-authored by Dr. Iakovlev cites a study[18] and states that "when microscopy was performed, results of the microscopic examinations usually did not explain the specific complications experienced by the patients."[19] In the same article Dr. Iakovlev and his co-authors also opined, "general human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications."[19] A second paper by Dr. Iakovlev reinforced his position and stated, "despite the long history of use and the large volume of explanted polypropylene devices, the causes and mechanisms of complications associated with the mesh remain incomplete."[20]

In the absence of countervailing studies or other significant evidence to allow clinic-pathologic correlations between histology and symptomatology (as discussed previously), reliable, scientifically grounded conclusions cannot be made between the histology found in an explanted mesh specimen and a patient's symptoms.

General Response to the Plaintiff's Expert.

Response to Dr. Iakovlev's Published J Biomed Mater Research paper (see Exhibit B).[20]

Research papers using surgical pathology specimens are often observational studies, and this paper is no exception. Observational studies in surgical pathology frequently consist of reviewing a cohort of cases from patients with a particular condition or disease, and then seeking to make correlations or associations with clinical symptomatology, findings, or outcome. Since the research surgical pathology material is derived from living human patients potential confounding variables can rarely be fully controlled or eliminated. In contrast, experimental pathology sets out with a hypothesis regarding the nature or cause of a particular event, and then conducts an experiment using animals or in vitro models while controlling for, or eliminating, possible confounding variables in order to provide data which will prove or disprove the working hypothesis. Observational studies are useful and may give rise to new hypotheses or speculation, but definitive conclusions often require experimentation or additional methodology. In surgical pathology research papers observations must be reported objectively in the "results section". Interpretation of the results and hypotheses generated from these interpretations must be restricted to the subsequent "discussion" section.

This paper by Dr. Iakovlev and colleagues does not adhere to good scientific practice. The paper mixes observations and their interpretations within the "results" section. In their introduction the authors state the purpose of their study: "…the fundamental question as to whether polypropylene degrades in vivo is still unresolved 50 years after its introduction…". Surprisingly, the authors answer this central question in only their second paragraph of Results with their statement, "histological slides showed a circumferential outer layer of degraded polypropylene" - even before all objective data from other methodologies has been reported.

This statement suggests that the authors were unable to separate objective results from subjective interpretations.

In the paper Dr. Iakovlev and colleagues used a number of techniques to examine explanted meshes. Among these techniques the authors used immunohistochemistry for the detection of immunoglobulin G (IgG) and myeloperoxidase. They report that, "There was no detectable level of IgG in the bark layer, while the immunoglobulin was deposited at its surface." Immunohistochemistry for myeloperoxidase showed similar findings. The authors conclude that this absence of staining indicated IgG "was not a component of the "bark" layer". The absence of immunohistochemical staining should be interpreted with great caution. Absent immunostaining may be attributable to a number of technical and biologic factors other than the complete absence of the protein (vide supra). The inability to detect a single protein is of very limited significance with respect to the nature of the "bark" since there are numerous proteins in the human blood and tissues. The authors make an unwarranted conclusion that the absence of one single protein, IgG, by immunohistochemistry "indicated incompatibility of the "bark" material with water-soluble proteins".

In this paper Dr. Iakovlev concludes that the mechanism leading to mesh-related complications is unclear, through his statement, " … the exact mechanisms of these late complications are yet to be understood,".

Response to Dr. Iakovlev's Expert Report.

In the introduction of his Summary opinion his expert report Dr. Iakovlev states that, "The mesh itself, as a foreign object, and the body reaction to the mesh damage the tissues in a critical anatomical location." In fact, tissues are damaged during the operative placement of the mesh and the subsequent foreign body and reparative reactions are the body's method to restore

tissue integrity. Tissue damage is a consequence of any surgery, including incontinence surgery, and would occur with non-mesh surgery for incontinence as well. Additional comments are made regarding specific components of the "Summary Opinion", related to histopathologic findings.

Dr. Iakovlev's report discusses an array of histological changes he claims to see in response to the implantation of mesh. He then attempts to correlate these histological findings to symptoms experienced by some patients. Strikingly, Dr. Iakovlev's opinion does not account for the rate at which any of these complications occur, despite his attempts to tie the healing response seen in nearly every patient to complications that occur in only a subset of those patients. Dr. Iakovlev has identified no histological feature unique to certain complications, no matter their frequency. Dr. Iakovlev's opinions are counter to professional organizations of physicians and surgeons who treat stress urinary incontinence who have recently reaffirmed their support for the use of polypropylene mid-urethral slings. For example, in May 2017 an authoritative and independent body, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), issued a position paper examining the benefits and potential harms of the use of mesh and included an assessment of possible complications.[21] RANZCOG has reiterated its recommendation for the use of polypropylene tapes in sling surgery for stress urinary incontinence, and also cited supporting evidence from the international Cochrane review Group on Urinary Continence and European Safety Commission's Scientific Committee on Emerging and Newly Identified Health Risks. This is an opinion that is shared by many other organizations, including the American Urogynecologic Society (AUGS); Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU); American College of Obstetricians and Gynecologists; Society of Gynecologic Surgeons; and Women's Health Foundation.[22] AUGS/SUFU noted in their position statement the decades long use of

polypropylene in the body and endorsed polypropylene mid-urethral slings as the standard of care, concluding "[t]his procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years . . ."

Dr. Iakovlev fails to acknowledge the low complications for mesh devices yet he himself co-authored a review article that reported chronic pain to occur in 1.8% of patients receiving a retropubic sling (such as TVT) and in 4.3% of patients receiving a transobturator sling (such as TVT-O).[19] Dr. Iakovlev also ignores a recent population based study published from Ontario, Canada, where both he and I work, showing the overall rate of mesh removal or revision of SUI slings to be 2.2% in the 59,887 women studied.[23]

Component 3 "Scar ingrowth and encapsulation describes the "formation of a mesh-scar plate". A "scar plate" is also described on page 7 of the Report, and the term used repeatedly in Component 9 and in captions of multiple figures (Figs 2c-f, 7d, e,f and 9a, b). The term "mesh-scar plate" and "scar plate" has been used by the author in prior publications. [20, 21] but has had very limited use or acceptance.[22] The term(s) suggest a hard, discrete mass. The characteristics that define a "mesh-scar plate" or "scar plate" are unclear. In particular what distinguishes the entity "mesh-scar plate" from any maturing or mature healing scar is not stated. The term "mesh-scar plate" is not an established entity within diagnostic pathology lexicon. Dr. Iakovlev goes on state that this "composite structure [i.e. mesh-scar plate] is stiffer than new mesh or scar tissue without mesh within", but no evidence is given to substantiate this conjecture.

Component 4 "Mesh contraction". No pathological evidence is given to support the opinion that, "Overtightened devices can compress organs and tissues". Dr. Iakovlev provides no histological evidence that can be used to evaluate mesh contraction, when studies have shown that mesh does not contract to any significant degree.[24, 25]

Component 9 “Stiff irregular mesh-scar plate under sensitive mucosa” states unequivocally that “… the mucosa is under risk for pain if it becomes compressed against the mesh-scar plate”. No evidence is presented to support this hypothesis.

Component 10 “Higher sensitivity for pain due to inflammation” states that, “ … tissues surrounding the mesh are more sensitive for pain than a scar without inflammation”. No evidence is presented to support this hypothesis. Indeed, as noted above a histopathologic study of pain of excised midurethral sling meshes found evidence to the contrary in that elevated levels of inflammation were present in excision specimens for voiding dysfunction as compared to those excised for pain and/or exposure.[10] A second study of explanted mesh following hernia recurrence concluded, “that there was little difference in inflammatory response in mesh removed for recurrence or chronic pain, contradicting the possibility of a specific tissue reaction as an underlying cause for either complication.” [9]

Component 11 “Tissue edema” states that”… pain due to swelling is present in cases of inflammation and trauma…” There is not a direct causation between oedema and the sensation of pain.

Component 12 “Involvement of striated (skeletal) muscle states that …”resultant pain can irritate the muscle and cause a spasm type contraction as it occurs in renal and biliary colic.”. No evidence is presented to support this conjecture.

Figures (1 – 3a, b,c, 4a,b,d,e, 6a-d, 7c, 9a,b, 10d-h) illustrate a normal healing (repair) process which is expected on the histopathologic examination of explanted meshes. However, some figure labels and captions imply an undesirable injury or outcome. For example, Figure 9a shows a scarred or thrombosed vessel, which is a normal finding at an operative site. This finding is labelled “obliterated vessel”. Similarly, Figure 9b shows another scarred or

thrombosed vessel, another normal finding at an operative site. This finding is labelled as "damaged artery". Vessel scarring is a normal component of a healing reaction, even in the absence of mesh. The captions of figures 7d-f all cite "damaged striated muscle" yet show striated muscle involved by scar, an expected finding at a healing operative site.

Figure 10b purports to show "curling of the edges of explanted sling materials." Whether these macroscopic images are of formalin-fixed specimens is not stated. As described above under "The practice of surgical pathology" the configuration of formalin-fixed tissues can be greatly altered during specimen fixation. Operative manipulation can also induce changes that were not present pre-operatively. The final configuration of an explanted mesh is attributable to multiple surgical and laboratory factors. In addition, Dr. Iakovlev is not able to determine whether the tissue reaction led to this configuration, it was implanted in this configuration, or whether the configuration came about during or after the excision procedure.

Sections 10d-h purport to show "complex folding" or "folding" of various meshes. Tissue configuration may be distorted by formalin fixation which could give rise to the appearance of folding. In addition, tangential sectioning in the histology lab of a single sheet of mesh with a wavy or wrinkled configuration could give rise to a more complex appearance.

Dr. Iakovlev provides several photomicrographs and numerous conclusions regarding what he calls degradation "bark". He extrapolates from his visual finding of an outer layer of material around the fiber to conclude this layer is degraded polypropylene. Dr. Iakovlev calls this material "bark", a term that has had very limited use, and may have originated in published literature in 2015. [Iakovlev – Exhibit B] Several previous histopathologic studies have not identified this finding as a notable feature in explanted mesh specimens. [9, 10, 13, 14, 16, 17] One published image shows apparent "bark" without any remark (Fig 1C). [18]

Dr. Iakovlev has presented a hypothesis and has not reliably proven this layer is in fact degraded polypropylene. His opinion is speculative and based upon his own article. His unequivocal conclusion that polypropylene mesh fibers have evidence of degradation in vivo due to the finding of "bark" is not supported by the current state of the research literature. The significance of "bark" with respect to degradation of polypropylene-based meshes remains an active area of research and has by no means been proven.[26, 27] Dr. Iakovlev's own publication has left open the question whether polypropylene degrades in the body, stating: "the question of whether polypropylene degrades *in vivo* has not been fully resolved despite decades of use."[19]

Dr. Iakovlev's theory and opinion regarding "bark" has not reliably ruled out the potential effects of the handling and processing of the mesh prior to his examination of it. Prior to a specimen arriving to the hands of a pathologist for a gross examination, the specimen will have gone through numerous changes, including physical excision and manipulation, and, typically, placement in a fixative. Then, prior to any pathologist's examination of the specimen under the microscope (and thus visualize the "bark"), it must be bathed in alcohol, xylene, and heated paraffin, and cut using a sharp blade. Thus, the tissue and mesh fibers viewed under Dr. Iakovlev's microscope are no longer in the same state as *in vivo*. The processing steps were established to maximize the analysis of tissue histology, not polypropylene. As noted above, histologic processing has been primarily developed to preserve tissue integrity only.

Finally, the issues of mesh degradation or "bark" were not even mentioned in the recent RANZCOG position paper, and the position statement released by AUGS and SUFU correctly noted that polypropylene has been used safely for many decades as a durable material, when they deemed polypropylene mid-urethral slings to be the standard of care.

Even if Dr. Iakovlev were correct and the “bark” contained degraded polypropylene, Dr. Iakovlev’s work and his litigation opinions do not provide medically reliable data that any such degradation “bark” has a clinically significant effect on patients. In his 2015 publication discussing the degradation layer, Dr. Iakovlev noted that the mechanism of the complications needs further study. Moreover, there is no evidence in the reaction surrounding these “bark” layers of any clinical effect, as the tissue reaction seen is a normal healing reaction to an implanted foreign body.

Conclusions;

There is no good histopathological evidence from Dr. Iakovlev’s research paper to support the hypothesis that the “bark” layer consists of polypropylene that degraded in vivo. The paper does not conform to acceptable scientific manuscript standards since objective findings are admixed with interpretation and conclusions. Dr. Iakovlev’s analysis in his expert report fails to offer more than hypothesis.

Although Dr. Iakovlev describes many histological features found in response to the implantation of mesh, these are expected findings after any surgery or implantation of a foreign body. Dr. Iakovlev attempts to correlate these histology findings to symptoms but, in general, neither a surgical or gynecologic pathologist can predict the clinical manifestations of a healing reaction or scar. Dr. Iakovlev’s statements or suggestions regarding the clinical manifestations attributed to histopathologic findings are conjectural and offered without any accepted evidentiary basis.

Fees

My billing rate is $500/hr.

Listing of cases in which testimony has been given in the last four years.

None

Terence J. Colgan

June 19, 2017

References:

1. Colgan TJ, Pron G, Mocarski EJM, Bennett JD, Asch MR, Common A. Pathologic features of uteri and leiomyomas following uterine artery embolization for leiomyomas. *Am J Surg Pathol* 2003; 27:167-77.
2. Colgan TJ, Shah R, Leyland N. Post-hysteroscopic ablation reaction: a histopathologic study of the effects of electrosurgical ablation. *Int J Gynecol Pathol* 1999; 18:325-31.
3. Rhodes A. Fixation of tissues. In: Suvarna SK, Layton C, Bancroft JD, eds. *Bancroft's Theory and Practice of Histological Techniques 7th Edition*. Churchill-Livingstone, London.
4. Drury RAB, Wallington EA. *Carleton's Histological Technique 4th Edition.* Oxford Press, New York, 1967. pg. 35.
5. Eltoum I, Fredenburgh J, Myers RB, Grizzle W. Introduction to the theory and practice of fixation of tissues. *J Histotechnol* 2001; 24(3): 173 - 90. http://dx.doi.org/10.1179/his.2001.24.3.173
6. Hopwood D. Fixatives and fixation: a review. *The Histochemical J* 1969; 1: 323 – 60
7. Engel KB, Moore HM. Effects of preanalytic variables on the detection of proteins by immunohistochemistry formalin-fixed paraffin-embedded tissue. *Arch Pathol Lab Med* 2011; 135: 537 – 43.
8. Kumar V, Abbas AK, Aster JC. *Robbins' Basic Pathology 9th Edition*. Elsevier-Saunders, 2013. Pgs.65 – 69
9. Klosterhalfen B, Junge K, Hermanns B, Klinge U. Influence of implantation interval on the long-term biocompatibility of surgical mesh. *Br J Surg* 2002; 89: 1043 – 48.

10. Hill AJ, Unger CA, Solomon ER et al. Histopathology of excised midurethral sling mesh. *Int Urogynecol J* 2015; 26: 591 – 5.

11. Falconer C, SoderbergM, Blomgren B, Ulmsten U. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. *Int Urogynecol J* 2001; S2: S19 – 23.

12. Wood AJ, Cozad MJ, Grant DA et al. Materials characterization and histological analysis of explanted polypropylene, PTFE, and PET hernia meshes from an individual patient. *J Mater Sci: Mater Med* 2013; 24: 1113 – 22.

13. Elmer C, Blomgren B, Falconer C et al. Histological inflammatory response to transvaginal polypropylene mesh for pelvic reconstructive surgery. *J Urol* 2009; 181: 1189 – 95.

14. Wang AC, Lee L, Lin C, Chen J. A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: a prospective case-controlled pilot study. *Am J Obstet Gynecol* 2004; 191: 1868 – 74.

15. Elmer C, Blomgren B, Falconer C et al. Histological inflammatory response to transvaginal polypropylene mesh for pelvic reconstructive surgery. J of Urol. 2009; 181: 1189 – 95.

16. Boulanger, L, Boukerrou M, lambaudies E et al. Tissue integration and tolerance to meshes in gynecologic surgery: an experimental study. Eur J Obstet Gynecol Repro Biol 2006; 125: 103 – 8.

17. Huffaker RK, Muir TW, Rao A et al. Histologic response of porcine collagen-coated polypropylene grafts in a rabbit vagina model. Am J Obstet Gynecol 2008; 198: 582 – 9.

18. Smith T. et al. Pathologic evaluation of explanted vaginal mesh: interdisciplinary experience from a referral centre. Female Pelvic Med. Reconstr. Surg. 2013;19, 238-41
19. Blaivas JG, Purohit RS, Benedon MS et al. Safety considerations for synthetic sling surgery. Nature Reviews Urology. 2015; 12: 495.
20. Iakovlev V, Guelcher SA, Bendavid R. Degradation of polypropylene in vivo: a microscopic analysis of meshes explanted from patients. J Biomed Mater Res Part B. 2017; 105: 237 – 248, Epub Aug 28 2015 PMID 26315946,
21. Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Position statement on midurethral slings (C-Gyn 32). May 2017.
22. Advancing Female Pelvic Medicine and Reconstructive Surgery, and the Society of Urodynamics Female Pelvic Medicine and Urogenital Reconstruction. Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence. June 2016.
23. Welk B, Al-Hothi H, Winick-Ng J. Removal or revision of vaginal mesh used for the treatment of stress urinary incontinence. JAMA Surg 2015; 150: 1167 – 75.
24. Bendavid R, Lou W, Koch A, Iakovlev V. Mesh-related SIN syndrome. Int J Clin Medicine 2014; 5: 807.
25. Klosterhalfen B, Junge K, Klinge U. The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices 2005; 2(1): 111.
26. Nilsson CG, Palva K, Aarnio R et al. Seventeen years' follow-up of the tension -free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013; 24: 1265 -9.
27. Dietz HP. Does the tension-free vaginal tape stay where you put it? Am J Obstet Gynecol 2003; 188: 950 – 3.

28. Thames SF, White JB, Ong KL. The myth: in vivo degradation of polypropylene-based meshes. Int Urogynecol J Sept 2 2016 e-pub
29. Talley AD, Rogers BR, Iakovlev VV et al. Oxidation and degradation of polypropylene transvaginal mesh. J Biomat Science, Polymer Edition. 2017 e-pub.

Exhibit A – Curriculum Vitae

Exhibit B – List of Materials.

Iakovlev VV, Guelcher SA, Bendavid R. Degradation of polypropylene in vivo: A microscopic analysis of meshes explanted from patients. J Biomed mater Res Part B 2017; 105: 237 – 248, Epub Aug 28 2015 PMID 26315946.

Expert Report of Dr. Vladimir Iakovlev, United States District Court, Southern District of West Virginia at Charleston. Master File NO. 2:12-MD-02327.